Ischemic Preconditioning Through Opening of Swelling-Activated Chloride Channels?

To the Editor:

We want to make the readers of Circulation Research aware of challenges that have arisen regarding an article that was recently published by Diaz et al1 in Circulation Research. They proposed the attractive idea that improved cellular volume control through opening of swelling-activated chloride channels was responsible for the infarct size reduction by ischemic preconditioning. Unfortunately, we were unable to reproduce most of their data.2 Specifically, we were unable (1) to induce consistently a swelling-induced chloride current using the same solutions and hypo-osmolarity (215 mOsm) as Diaz et al in isolated rabbit cardiomyocytes, and instead had to use the solutions and hypo-osmolarity (167 mOsm) in the original report of Wong et al; (2) to find a current amplitude (60 mA/pF at +60 mV) of the magnitude reported by Diaz et al, even with the stronger hypo-osmotic stimulus and elicited a current amplitude of only an order of magnitude less, consistent however, with several prior studies as referenced in our article; (3) to block the swelling-induced chloride currents with drugs at the low concentrations reported by Diaz et al, and had to use 100-fold higher concentrations, which proved toxic in whole hearts, again consistent with prior studies; and (4) to prevent infarct size reduction by ischemic preconditioning in isolated rabbit hearts at the drug concentrations reported by Diaz et al.

Diaz et al1 have published a response in the Journal of Molecular and Cellular Cardiology that addresses our challenge. We have further responded to their new arguments and clarifications with our own rejoinder.4 The details of this exchange will not be repeated here, but all interested readers of the original study1 are hereby alerted to the controversy.

We still believe that improved cellular volume control is an attractive effector candidate of ischemic preconditioning, but this hypothesis remains to be adequately tested.

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